REMARKS

Claims 1, 8, 10 and 20 are amended without prejudice or disclaimer to correct typographical errors. No new matter has been added.

Claims 1-20 are pending and stand rejected as obvious. For the following reasons, reconsideration and withdrawal of the rejection is respectfully urged.

The Claimed Invention

Applicants claim a process for preparing a pharmaceutical formulation of 5-chloro-*N*-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide, also known as rivaroxaban, in hydrophilized form by moist granulation and formulations of rivaroxaban in which rivaroxaban is in hydrophilized form.

Rivaroxaban is an orally administrable inhibitor of blood clotting factor Xa. Rivaroxaban has been approved for use in Europe for prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. The discovery and development of rivaroxaban marked a very significant breakthrough for treatment of patients at risk for thromboembolic disorders. Recognizing this, in 2009 the German Federal President awarded the German Future Prize, the highest innovation award in Germany, to three scientists involved in the development of rivaroxaban.

The present invention is based on the discovery that although tablets of rivaroxaban prepared by moist granulation had a very similar in vitro release rate as tablets prepared by direct tabletting without moist granulation, nevertheless the tablets prepared by moist granulation had a marked advantage in absorption and thus a bioavailability increase of about 35%. Application, page 11.

The Rejection

Claims 1-20 are pending and are rejected as obvious over Straub et al. (US Pat. Pub. 20030153610) in view of Yamamoto et al. (US Patent 6,514,529) and Martin et al. (US Patent 4,344,934). The Office relies upon Straub et al. for disclosing the active compound. Yamamoto et al. and Martin et al. are relied upon for allegedly showing other active agents formulated in hydrophilized and crystalline form by moist granulation and converted into a pharmaceutical formulation with pharmaceutically acceptable excipients such as hydroxypropylmethylcellulose

(HPMC). The Office Action states that one of ordinary skill in the art would be motivated to formulate rivaroxaban according to the methods of Yamamoto et al. and Martin et al. with a reasonable expectation of success because allegedly both references teach increased bioavailability from such a formulation. Final Office Action, page 6.

Applicants respectfully disagree. As explained fully below, Applicants respectfully submit that one of ordinary skill in the art at the time of the invention would not have found the invention obvious over the cited references.

Yamamoto et al.

One of Ordinary Skill in Pharmaceutics Would Not Have Looked to Yamamoto et al. for Guidance to Formulate Rivaroxaban.

The Patent Office argues that because Yamamoto et al. is chiefly concerned with formulating oxazolidinone agents, the person of ordinary skill looking to formulate rivaroxaban, another oxazolidinone agent, would look to Yamamoto et al. for guidance and have a reasonable expectation of success with the modification. The Applicants previously pointed out the very significant solubility difference between linezolid, the compound used in the examples of Yamamoto et al., and rivaroxaban. However, the Office still rejected the claims, stating that because Yamamoto et al. is not directed to only one agent with one solubility, and because Yamamoto et al. never mentions solubility at all, one of ordinary skill would not be particularly concerned with the solubility differences but instead would rely on similarity in chemical structure. Final Office Action, page 8.

Applicants respectfully disagree. To one skilled in the art of pharmaceutical dosage form design, the major considerations in the design of dosage forms ***do not include chemical structure***. For example, the highly regarded textbook "Pharmaceutics, The Science of Dosage Form Design" begins with introducing the major considerations in dosage design:

> The [first] chapter explains that there are ***three major considerations*** in the ***design of dosage forms***:
>
> 1. ***The physicochemical properties of the drug itself,***
> 2. Biopharmaceutical considerations, such as how the route of administration of a dosage form affects the rate and extent of drug absorption into the body, and

3. Therapeutic considerations of the disease state to be treated, which in turn decide the most suitable type of dosage form, possible routes of administration and the most suitable duration of action and dose frequency for the drug in question.

Michael E. Aulton (editor), published by Elsevier Ltd (2002), p. xiii, copies of referenced pages submitted with Information Disclosure Statement (IDS) filed today, emphasis added. Aulton provides a table listing the properties of drug substances important in dosage form design. These properties ***do not include chemical structure.*** The properties are particle size, with surface area; solubility; dissolution; partition coefficient; ionization constant; crystal properties, including polymorphism; stability and organoleptic. Id., Table 1.3 on p. 7. Furthermore, Aulton specifies what is meant by the physical and chemical properties of a drug substance: "These properties, such as ***dissolution***, crystal size and polymorphic form, solid-state stability and drug – additive interactions, can have profound effects on the physiological availability and physical and chemical stability of the drug." Id. at p. 6, emphasis added.

Aulton is not alone in teaching the importance of physicochemical properties and not chemical structure in drug formulation. The FDA proposed a biopharmaceutics classification system ("BCS") as a bioavailability-bioequivalence regulatory guideline that recognizes that ***drug dissolution and gastro intestinal permeability*** are the ***fundamental parameters*** controlling the rate and extent of drug absorption. See Jain et al., "Pharmaceutical product development technologies based on the biopharmaceutical classification system," Pharmazie 64 (2009) 8, pp. 483-490 at p. 483, submitted with the IDS filed today, and the FDA "Biopharmaceuticals Classification System (BCS) Guidance," submitted with the IDS filed November 1, 2010. Under the BCS, drugs are placed in one of four classes based on physicochemical properties: class 1: high solubility-high permeability; class 2: low solubility-high permeability; class 3: high solubility-low permeability; and class 4: low solubility-low permeability. Id. at p. 484.

Thus, one of ordinary skill in the art preparing a new dosage form would have identified the physicochemical properties of a drug, such as solubility, as of primary importance. Similarity in core chemical structure is <u>not</u> a property that these references teach as indicative of similarities in formulation. One of ordinary skill therefore would not have been motivated to use a

formulation for another drug that might have a similar core structural element but that has significantly different solubility, such as the case with linezolid and rivaroxaban.

Rather, one of ordinary skill in the art looking to formulate rivaroxaban would look to its solubility. "Prior to the development of these three major dosage forms [tablets, capsules and injections] it is essential that certain ***fundamental*** physical and chemical properties of the drug molecule and other ***derived*** properties of the drug powder are determined." Aulton (ed.), chapter 8, James Wells, "Pharmaceutical preformulation: the physicochemical properties of drug substance," p. 114 (emphasis in original), submitted with IDS filed today. "The need for adequate drug solubility cannot be overemphasized." Id. at p. 138.

Rivaroxaban is poorly water soluble, having only 7 mg/l solubility. Specification, page 1 line 13. In contrast, Yamamoto et al. chiefly is concerned with formulations of linezolid, which has much greater water solubility than rivaroxaban. Linezolid has a solubility of 3000 mg/l, which is more than 400 fold more water soluble than rivaroxaban.

Furthermore, this significant difference in solubility results in linezolid being categorized in the British Pharmacopeia 2009 as "slightly soluble," whereas rivaroxaban is characterized as "practically insoluble." See British Pharmacopeia 2009, relevant pages submitted on November 1, 2010.

A person of ordinary skill in the art would see this great difference in solubility between the main drug in Yamamoto et al. and rivaroxaban and would not be motivated to substitute rivaroxaban for linezolid. One of ordinary skill would not be swayed by the presence of a similar core structure because the field looks to physicochemical properties, and especially solubility, to design dosage formulations. Where physicochemical properties are very different, one of ordinary skill would not expect successful substitution.

In view of the above comments and the references submitted today, Applicants respectfully request that the Patent Office reconsider and withdraw its finding that Yamamoto et al. would be relied upon to formulate rivaroxaban, and also that even if it were looked to, one of ordinary skill would have had a reasonable expectation of success in solving the formulation problems presented by poorly soluble rivaroxaban with the formulations in Yamamoto et al.

The Patent Office also stated that Yamamoto et al. is not directed to only one specific agent with one very specific solubility. Indeed, Yamamoto states under the Summary of

Invention that the tablet contains "antibacterial oxazolidinone" (col 1 lines 27-31) and provides two oxazolidinones in addition to linezolid as preferred agents for the formulation (col 2 lines 5-53 and col 3 line 65 to col 4 line 2). Yet the reference does not provide any direct teaching on oxazolidinones other than suggested formulations for linezolid (see, e.g., col 4 lines 15-64 with four suggested linezolid formulations). In fact, Yamamoto et al does not provide any actual data at all to show that the formulations worked. No dissolution data or bioavailability data is provided for any formulation. Yamamoto et al. states that there is a need for a tablet formulation which permits high drug load with blood levels similar to IV administration (col. 1 lines 24-25). Yet Yamamoto et al. does not publish any evidence that these goals were obtained. An ordinary scientist would look for actual data rather than general statements of the goals of the formulation before having a reasonable expectation of success with the formulation.

Also, for the same reasons mentioned above, an ordinary skilled scientist would look to the physicochemical properties of the other compounds that Yamamoto et al. discloses may be used in its formulations and not rely on structural similarity. Yamamoto et al. only presents structural similarity, not physicochemical similarity between the three specifically named drug compounds. Accordingly, the person of ordinary skill would not have a reasonable expectation of success with substituting rivaroxaban for one of these other named compounds for which no physicochemical data is presented.

The Rejection Incorrectly Describes Yamamoto's Disclosure.

Applicants respectfully disagree with the Patent Office's description of Yamamoto et al. The Office alleges that Yamamoto et al. teaches to take the crystalline linezolid, suspend it in granulating liquid, and introduce it into fluidized bed granulation. Final Office Action, page 4. It is respectfully submitted that the reference does ***not*** teach suspending linezolid in a granulating liquid, or using fluidized bed granulation.

As shown in a flow chart in column 10 lines 1-33 of Yamamoto et al., linezolid is not suspended in granulating liquid but rather is pre-blended in a high shear mixer. Furthermore, granulation does not occur in a fluidized bed. The linezolid formulation is granulated using the high shear mixer, as shown at column 10 line 10: "Granulate using the high shear mixer." A

fluidized bed is not used for granulation. Drying, not wet granulation, occurs in a fluid bed dryer. See Col. 10 lines 4-14 and col. 8 lines 27-40.

Although the Office Action specifically refers to many passages in Yamamoto et al., only the reference to col. 5 lines 52-67 or 55-67 concerns the granulation step. This passage, however, states that granulation is performed in ***a high shear mixer***, not a fluid bed granulator as the Office asserts. This section of Yamamoto et al. also discloses that a fluid bed is used for drying, not for wet granulation: "Following granulation the granulation is dried using suitable equipment, such as a fluid bed dryer." Col. 5 lines 66-67. Accordingly, the passages cited by the Patent Office as supporting this alleged disclosure do not actually show it.

Accordingly, the Office's reliance on Yamamoto et al. to show these elements of dependent claims 2 and 5 is misplaced.

The Office Action also states that Yamamoto et al. discloses an oxazolidinone compound and HPMC present in a concentration of 1-60% and 1-15% at column 9 lines 10-30. Yet at this section of Yamamoto et al., one specific linezolid tablet formulation is provided and no ranges of components are provided. Accordingly, the Patent Office has not shown where these ranges recited in dependent claims 11 and 15 are taught.

Martin et al.

When Martin et al. is Read as a Whole, it Does Not Teach or Suggest the Claimed Invention, Provide a Motivation to Substitute Rivaroxaban in Its Process, or Provide a Reasonable Expectation of Success if Such Substitution Was Made.

The Patent Office asserts that Martin et al. discloses a process for preparing a solid, oral pharmaceutical composition of an active agent in hydrophilized form by moist granulation. Final Office Action, p. 5. The Office asserts that because Martin et al. teaches that poorly water-soluble antibiotics can be formulated with its processes to significantly increase bioavailability, one of ordinary skill would have substituted poorly soluble rivaroxaban into the Martin et al. process and obtained the presently claimed invention. Final Office Action, p. 6.

Applicants respectfully submit that this argument is based on hindsight, using Applicants' specification as a blueprint. It also ignores the law that each prior art reference must be evaluated as a whole. *In re Evanega,* 829 F.2d 110 (Fed. Cir. 1987). It is impermissible to use the inventor's application as a template from which to go into a prior art reference and pick and

choose only so much of it as will support the rejection to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. *Bausch & Lomb, Inc. v. Barnes-Hind, Inc.*, 796 F.2d 443 (Fed. Cir. 1986).

When Martin et al. is evaluated as an entirety, it concerns a process for obtaining ultramicronized griseofulvin. The process has many steps, with several options available at certain of the steps. Martin et al. discloses a process that starts first with a mixture or solution of the drug with a polymer. Col. 5 lines 29-44. The mixture may be formed by melt mixing or by solution in a mutual solvent, which is different than wet granulation. Col. 5 lines 34-37 and col. 3 lines 22-24. After this, the mixture is dried by spray-drying, flash evaporation or air drying. Col. 5 lines 45-47. The melt-mix product is dried by cooling. Col. 5 line 50. The dried product is then ground or milled into powder form. Col. 5 lines 50-53.

The powdered drug-polymer mixture is then treated with a wetting solution by forming a slurry, wet granulation or paste mixture of the powdered drug polymer with the wetting solution. Martin et al. believe that the wetting solution treatment may ensure ultramicrosized crystals and the breakup of clusters of such crystals so they disperse spontaneously when exposed to water. Col. 5 lines 54-68. The treated mixture is then dried, and if necessary, it is milled, screened or ground prior to formulating into suitable dosage forms with suitable excipients. Col. 6 lines 9-12.

The examples show generally faster dissolution rate with the ***ultramicronized*** griseofulvin produced using this process than with ***microsized*** griseofulvin or untreated griseofulvin. The relative bioavailability of the griseofulvin produced using two different polymers according to this process showed "no statistically significant differences" between the griseofulvin ultramicronized by the disclosed process and the ultramicronized griseofulvin on the market, presumably prepared by a different process. See Col 13 line 53 to col. 14 line 15.

Accordingly, Martin et al. discloses to the person of skill in the art another process to make ultramicronized griseofulvin.

It is only by using hindsight that Martin et al. can be identified as having any significance whatsoever to the problem of formulating poorly soluble rivaroxaban, let alone as suggesting that hydrophilization of rivaroxaban by moist granulation is the solution. As discussed above, the person of ordinary skill in the art reading Martin et al. ***as a whole*** sees a method for making

ultramicronized griseofulvin particles using steps of melting or dissolving, followed by drying, wetting, drying again, and formulating.

The Patent Office refers to general statements in Martin et al. that its teaching applies drugs other than griseofulvin. Office Action, page 9. Admittedly, there are passages in Martin et al. where it is suggested that the teaching of the patent is also applicable to other drugs. However, a person of ordinary skill in the art would pay no heed to these suggestions. This is because apart from these general statements, Martin et al. contains no concrete indication that this asserted generalization is at all possible. Examples 1-17 without exception all relate to griseofulvin. In order for a reasonable person to assume some generalized applicability of the teaching, the person would expect supplementary examples with other drugs. But such other examples are completely missing in Martin et al.

Because of the lack of technical support for the generalizations of broader use for the disclosed process, one of ordinary skill in formulating dosages would not be led to substitute rivaroxaban in the Martin et al. process. Furthermore, even assuming one was motivated, there would be no grounds for a reasonable expectation of success with this substitution where only data for one drug is provided.

The Final Office Action found a motivation to use Martin et al. because Martin et al. allegedly discloses a process that results in "significantly increased active agent bioavailability." Office Action, p. 6. Yet upon close reading of Martin et al. it is seen that the "increased" bioavailability obtained by its process is not statistically different from the bioavailability of the ultramicrosized griseofulvin on the market already. Col. 14 lines 3-5. Although the title of Martin et al. states that the composition has "enhanced bioavailability," the composition is shown in the examples to achieve the same bioavailability as other ultramicrosized formulations. Accordingly, the bioavailability cannot be said to be "increased" because it is the same as prior formulations. Thus, the asserted motivation to use rivaroxaban in Martin et al. for the "increased" bioavailability is not really present when the data in the examples is taken into consideration.

The examples in Martin et al. show better ***dissolution rate*** with its ultramicronized griseofulvin compared to microsized griseofulvin, but do not show whether the ***bioavailability*** is improved over microsized griseofulvin. The only example concerning improved bioavailability

is the comparative example discussed above showing no statistically significant difference between the ***ultramicronized*** product made by the Martin et al. process and the ***ultramicronized*** griseofulvin on the market. In contrast to Martin's griseofulvin, rivaroxaban tablets prepared by direct tabletting already had a good dissolution profile. Specification, pp. 10-11. Because the tablet dissolution rate was already good, the skilled artisan would not have been motivated to follow the process in Martin et al., which is taught to improve dissolution rate. The reasonable artisan would not have had any expectation of success in using the Martin et al. teachings to improve bioavailability, because dissolution rate was already good. In fact, because the examples in Martin et al. only show improvement in dissolution rate, not bioavailability, one of ordinary skill would have been led away from following its teachings because rivaroxaban already had a good dissolution profile when directly tabletted.

In sum, when read as a whole, Martin et al. does not suggest hydrophilization of rivaroxaban, and its general statements of application to other drugs are not supported by concrete indications that this would be successful, nor are its assertions of "increased" bioavailability supported by comparisons to formulations having lower bioavailability. Martin et al. suggests solutions to improving dissolution rate. Because dissolution rate was not a problem for rivaroxaban, the person of skill in the art would not have been motivated to use rivaroxaban in the processes of Martin et al.

Accordingly, for these reasons it is urged that the Patent Office reconsider the obviousness rejection over Martin et al. in combination with other references and withdraw the rejection.

CONCLUSION

For these reasons, reconsideration of the obviousness rejection and allowance of the claims is respectfully requested. This Amendment is filed with a Request for Continued Examination, a fee for a one-month extension of time and an Information Disclosure Statement. The fees for the RCE and extension are authorized to be charged to the undersigned's credit card in the electronic submission today. No additional fees are believed due with the filing of this

paper. However, if an additional fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987- 00043-US from which the undersigned is authorized to draw.

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